# The evolution of the knowledge of cat and dog coccidia

J. P. DUBEY*

*United States Department of Agriculture, Agricultural Research Service, Animal and Natural Resources Institute, Animal Parasitic Diseases Laboratory, Building 1001, Beltsville, MD 20705-2350, USA*

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SUMMARY

Before the discovery of *Toxoplasma gondii* as a coccidium of the cat in 1970, cat and dog coccidia were classified in the genus *Isospora* and considered of little clinical or zoonotic significance. Since 1970, several new (*Hammondia* sp., *Neospora* sp.) and previously described species, including *Sarcocystis*, *Besnoitia*, and *Cryptosporidium* have been found as coccidians of cats and dogs with clinical and zoonotic significance. In the present paper I review salient features of the evolution of cat and dog coccidia.

Key words: *Toxoplasma gondii*, protozoa, coccidia, cat, dog, zoonosis.

## INTRODUCTION

Although coccidia are one of the first parasitic protozoa discovered, little was known of their importance in cats and dogs until 1970 (Levine and Ivens, 1981). An explosion of information has occurred on this topic in the last 40 years and I had the fortune of being associated with many of the studies in this field (Table 1). In the present special issue of the journal some of these personal experiences are recalled. My objective is not to discuss controversies regarding nomenclature or to seek or give priorities to works by different groups. The present discussion relates to faecally transmitted coccidians of domestic cats (*Felis domesticus*) and domestic dogs (*Canis familiaris*).

## EARLY HISTORY OF CAT AND DOG COCCIDIA

### *Coccidia split into three groups*

Until the report of Wenyon (1923), only 1 species of coccidium was thought to be present in the faeces of cats and dogs. Wenyon (1923, 1926) reviewed earlier literature and concluded that Grassi (1879) probably named a coccidium in the cat now regarded as *Coccidium rivolta*, and Stiles (1891) named a parasite *Coccidium bigemina* first from the dog (Table 1). Lühe (1906) transferred these parasites to the genus *Isospora*.

Wenyon (1923) made the first distinction that there were at least 3 species of coccidia in cats and dogs, based on the oocyst size: (1) large oocyst measuring approximately 40 long $\mu$m; (2) medium oocyst size measuring 25 $\mu$m long; (3) small oocyst size measuring 10 $\mu$m long.

Wenyon (1923) named the coccidium with large oocysts as *Isospora felis* and partly described its endogenous stages in the intestine of the cat.

*The large oocyst size coccidium split into two species*. Nemeséri (1959, 1960) probably was the first to conduct cross-transmission of dog and cat coccidia. He could not transmit the large coccidium from the dog to the cat and named the dog parasite as a new species, *Isospora canis*.

Shah (1970, 1971), who was my teacher in the veterinary school, made the first definitive study in this field. He micro-isolated a single *I. felis* oocyst, produced a cloned isolate by feeding the oocyst to a coccidia-free kitten, re-described its oocysts, and described the asexual and sexual stages of the parasite in the intestine of the kittens. He also showed that the parasite was not transmissible to dogs. Lepp and Todd (1974) described asexual and sexual stages of *I. canis* using cloned parasites.

*The medium oocyst size coccidium split into several species*. Coccidia are ubiquitous and it is difficult to raise cats and dogs coccidia-free. In the 1960s, it became possible to raise parasite-free cats and dogs by using Caesarian section and germ-free isolators. Fortunately for me, I got a professorship in veterinary parasitology in 1973 at the Ohio State University, Columbus, Ohio, where cats and dogs were raised in isolators. I used these pets for cross-transmission studies with cat and dog coccidia. I was unable to infect dogs with *Isospora rivolta*-like parasite from cats, and named the dog parasite, *Isospora ohioensis* (Dubey, 1975), and retained the

* Tel: +1 301 504 8128. Fax: +1 301 504 9222. E-mail: jitender.dubey@ars.usda.gov

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Table 1. Knowledge of the evolution of coccidia of cats and dogs

| Year | Observation | Reference |
|---|---|---|
| 1879 | *Coccidium rivolta* oocysts found in faeces of cat | Grassi (1879) |
| 1891 | *Coccidium bigemina* found in the intestine of dog | Stiles (1891) |
| 1906 | *Coccidium bigemina* transferred to genus *Isospora* | Lühe (1906) |
| 1923 | *Isospora felis* n.sp. oocysts found in faeces of cat | Wenyon (1923) |
| 1959–1960 | *Isospora canis* n.sp. described in dog feces and found non transmissible to cats | Nemeséri (1959, 1960) |
| 1970 | *Isospora felis* found not transmissible to dogs | Shah (1970) |
| 1970 | *Toxoplasma gondii* found to be coccidum of cats | Hutchison *et al*. (1970); Frenkel *et al*. (1970); Dubey *et al*. (1970*a*, *b*); Sheffield and Melton (1970); Overdulve (1970). |
| 1971 | Endogenous stages of *Isospora felis* described in cat small intestine using cloned oocysts | Shah (1971) |
| 1972 | Extra-intestinal stages (tissue cyst) of *Isospora felis* and *Isospora rivolta* found | Frenkel and Dubey (1972) |
| 1972 | *Sarcocystis* spp. found to have gametogony (oocysts) in the intestine of cats and dogs | Rommel *et al*. (1972); Heydorn and Rommel (1972) |
| 1975 | *Isospora ohioensis* n.sp. of the dog proposed and separated from *I. rivolta* of the cat | Dubey (1975) |
| 1975 | *Hammondia hammondi*. n.gen., n.sp., described as new coccidium of cats | Frenkel and Dubey (1975) |
| 1975 | *Besnoitia* sp. found to be coccidium of cats | Wallace and Frenkel (1975) |
| 1977 | *Cystoisospora n.g*. proposed for isosporan species with a unizoite tissue cyst | Frenkel (1977) |
| 1978 | Complete life cycle of *Isospora ohioensis* described using cloned oocysts | Dubey (1978) |
| 1978 | *Isospora neorivolta* n.sp. of the dog proposed and separated from *I. ohioensis* | Dubey and Mahrt (1978) |
| 1978 | *Isospora burrowsi* n.sp. of the dog proposed | Trayser and Todd (1978) |
| 1979 | Complete life cycle of *Isospora rivolta* of cat described | Dubey (1979) |
| 1979 | *Cryptosporidium felis*, new species found in cats | Iseki (1979) |
| 1921 | *Cryptosporidium canis*, new species found in dogs | Fayer *et al*. (2001) |
| 1988 | *Neospora caninum*, n.g., n.sp. proposed as a cause of toxoplasmosis-like illness in dogs | Dubey *et al*. (1988) |
| 1998 | *Neospora caninum* oocysts found in dog faeces | McAllister *et al*. (1998) |

designation *I. rivolta* for the cat parasite. I also described the first complete life cycles of a canine (*I. ohioensis* in the dog, Dubey, 1978) and a feline coccidium (*I. rivolta* in the cat, Dubey, 1979).

Before the recognition of *I. rivolta* and *I. ohioensis* as separate species, Mahrt (1967, 1968) had very carefully studied the life cycle of an *I. rivolta*-like parasite of the dog. During the studies on the development of *I. ohioensis*, I realized that there were differences in the endogenous stages of *I. ohioensis* and *I. rivolta* in the dog, the former located in the surface epithelium and the latter in the lamina propria. I re-examined all histological sections from dogs that Professor Mahrt made available to me and we named the parasite studied by Mahrt as *Isospora neorivolta* (Dubey and Mahrt, 1978). Trayser and Todd (1978) described another species, *Isospora burrowsi*, from the dog. There is an overlap in size of the oocysts and in the location in the intestine of dogs among *I. ohioensis*, *I. neorivolta*, and *I. burrowsi*, therefore, this group is sometimes called *I. ohioensis*-like parasites.

## THE SMALL-SIZED OOCYSTS, *COCCIDIUM BIGEMINA*, AND EXPLOSION OF INFORMATION

As said earlier, this parasite was first named by Stiles (1891) who found it as a fully sporulated oocyst in the lamina propria of the dog. Wenyon (1923, 1926) reviewed earlier literature and stated that both forms (in the epithelium and in the lamina propria) were found in dogs and cats; both unsporulated and

sporulated forms were regarded as the same parasite, *I. bigemina*.

### *Discovery of* Toxoplasma gondii *life cycle*

The most thrilling discovery in my life was made in 1970, when cats fed *Toxoplasma gondii* tissue cysts shed *I. bigemina*-like oocysts, and animals fed these oocysts died of toxoplasmosis. Several groups of workers (Table 1) independently and around the same time (see Dubey, 2008) found *T. gondii* oocysts in cat faeces (Hutchison *et al.* 1970; Frenkel *et al.* 1970; Dubey *et al.* 1970*a*, *b*; Sheffield and Melton, 1970; Overdulve, 1970).

Although the discovery of the oocyst stage in the life cycle of a coccidian parasite would be expected to prove *T. gondii* to be a coccidian parasite, this was a big challenge at that time for the following reasons. First, faecal infectivity (oocyst) was linked with *Toxocara* infectivity (Hutchison, 1965, 1967). Second, the oocyst had been called a new cyst (Work and Hutchison, 1969). *Toxoplasma gondii* oocysts were morphologically identical to oocysts of the previously described coccidian parasite (*I. bigemina*) of cats and dogs. In light of these facts, the evidence provided by us to link *T. gondii* oocysts to faecal infectivity is noteworthy (Frenkel *et al.* 1970; Dubey *et al.* 1970*a*). We subjected the newly discovered faecal stage (oocyst) to the following mutually independent tests to accumulate critical evidence for or against its being identical to *T. gondii* (Dubey *et al.* 1970*a*). (i) Newborn kittens and littermate controls were used to avoid as far as possible pre-existing coccidial infections. (ii) Comparison of the development of oocysts and of infectivity in relation to heat, cold, oxygenation and chemicals. (iii) Comparison by filtration of the size of the infectious entity with oocyst size. (iv) Comparison of the density characteristics of oocysts and of infectivity. (v) Comparison of the electrophoretic characteristics of oocysts and infectivity. (vi) Antigenic comparison of oocysts with the standard RH strain of *Toxoplasma* by means of the fluorescent antibody test. (vii) Identification of the endogenous cycle preceding the development of oocysts, and linking it antigenically to *Toxoplasma* infectivity of oocysts before and after excystation. (viii) Comparison of the appearance of oocysts and *Toxoplasma* infectivity in the faeces of cats after feeding of cysts, trophozoites, and oocysts (Dubey *et al.* 1970*a*).

In retrospect, the discovery and characterization of the *T. gondii* oocyst in cat faeces was also delayed because until 1970 coccidian oocysts were sporulated in 2·5% potassium dichromate. Chromation of the oocyst wall interfered with excystation of the sporozoites when oocysts were fed to mice and thus the mouse infectivity titre of the oocysts was lower than expected from the number of oocysts administered (Dubey *et al.* 1970*a*). These findings led to the use of 2% sulfuric acid as the best medium for sporulation and storage of *T. gondii* oocysts. Unlike dichromate, which was difficult to remove from oocysts, sulfuric acid could be easily neutralized and the oocysts could be inoculated directly into mice (Dubey and Frenkel, 1973). Unlike other coccidians, *T. gondii* oocysts were found to excyst efficiently when inoculated parenterally into mice. This observation alleviated the need for oral inoculation for the bioassay of oocysts (Dubey and Frenkel, 1973).

The medical and biological significance of the discovery of the life cycle of *T. gondii* described above is that unlike the previous view that coccidia were host specific (confined to 1 host) and site specific (confined to intestine and faeces), *T. gondii* infected virtually all warm-blooded animals including humans and virtually any cell of the body. However, it retained an evolutionary characteristic of completing the oocyst phase only in 1 host (cats, not only domestic but other felids as well).

Although *T. gondii* has a worldwide distribution and perhaps the widest host range of any parasite, there is only 1 species, *gondii* in the genus, *Toxoplasma*. Why some people develop clinical toxoplasmosis whereas most remain asymptomatic is largely unknown. During the 1980s and 1990s methods were developed to recognize genetic differences among *T. gondii* isolates from humans and animals (Pfefferkorn and Pfefferkorn, 1980; Dardé *et al.* 1987; Tibayrenc *et al.* 1991; Sibley *et al.* 1992; Howe and Sibley, 1995). Mapping of *T. gondii* genes was achieved recently (Khan *et al.* 2005), and undoubtedly will help in the search for better antigens for diagnosis and protection, and mechanism of disease. Until recently, *T. gondii* was considered clonal with very little genetic variability (Howe and Sibley, 1995). Lehmann *et al.* (2006) made the first indepth study of genetic variability among more than 275 *T. gondii* isolates obtained worldwide from one host (free-range chicken) and in one laboratory (Dubey *et al.* 2002*c*) and found geographical differences, with some isolates being confined to Brazil whereas others being worldwide in distribution. Recent studies using a large numbers of isolates from Brazil and the USA indicated higher genetic diversity than previously recognized (Dubey and Su, 2009). It is hoped that further genetic studies on *T. gondii* isolates from various sources may lead to identification of sources of infections for humans.

### *Discovery of* Sarcocystis *life cycle*

Soon after the discovery of the life cycle of *T. gondii*, Heydorn and Rommel (1972) and Rommel *et al.* (1972) found that dogs and cats fed *Sarcocystis* cysts (sarcocysts) developed gamonts and oocysts in the lamina propria, and these oocysts, unlike previously known coccidia, sporulated *in situ*. Thus, the mystery of the sporulated oocysts in the lamina propria

previously found by many scientists earlier became clear. To my knowledge there are at least 10 species of *Sarcocystis* that are found in cat faeces, and at least 21 in dog faeces (Dubey *et al*. 1989, and many more would be found in the future (Dubey and Odening, 2001). It is almost impossible to distinguish *Sarcocystis* species based on the morphology of oocysts (Dubey *et al*. 1989). Therefore, it is futile to speculate which species was present in the sample examined by Stiles (1891). On a personal note, Dr J. K. Frenkel and I also attempted to search for *Sarcocystis* oocysts in the faeces of cats in 1970 but were unsuccessful because we fed sarcocysts from the heart of cattle to cats. In retrospect, now we know that cattle have 3 species of *Sarcocystis*, *S. cruzi* (transmitted only through canids), *S. hirsuta* (transmissible via cats), and *S. hominis* (transmissible via humans and primates) and *S. hirsuta* transmitted by cats does not form sarcocysts in the heart of cattle (Dubey *et al*. 1989).

### *Discovery of new genera,* Hammondia, Neospora, *and finding of oocysts in cats and dogs*

Frenkel and Dubey (1975) described a new parasite, *Hammondia hammondi*. This parasite is morphologically similar to *T. gondii* but with a different life cycle. Unlike, *T. gondii*, it is non-pathogenic, and has an obligatory 2-host life cycle. Its oocysts resemble *T. gondii* in size and structure (Dubey and Sreekumar, 2003; Schares *et al*. 2008). A similar parasite was found to cycle through dogs (Heydorn, 1973; Dubey and Fayer, 1976) and was named *Hammondia heydorni* (Dubey, 1977; Dubey *et al*. 2002*b*). Although *T. gondii* and *H. hammondi* oocysts are produced by cats, dogs do ingest cat faeces, and thus all three species, *T. gondii, H. hammondi*, and *H. heydorni* can be present in faeces of naturally-infected dogs (Schares *et al*. 2005).

A new parasite, *Neospora caninum*, was described in 1988 (Dubey *et al*. 1988). Until 1988, this parasite was misdiagnosed as *T. gondii* (Dubey *et al*. 2002*b*). Its veterinary importance became known a few years later when it was found to cause abortion in cattle and clinical disease in many other species of animals (Dubey *et al*. 2007). Its oocyst was discovered in 1998 when dogs, but not cats, fed tissue cysts shed oocysts (McAllister *et al*. 1998). Cats are not definitive hosts for *N. caninum* (McAllister *et al*. 1998). Unlike, *T. gondii*, *N. caninum* is regarded as a major pathogen of cattle and dogs (Dubey *et al*. 2007).

### *Discovery of the life cycle of* Besnoitia

*Besnoitia* spp. are parasites of livestock and wild animals. Some species of *Besnoitia* cause economic losses to farmers in some parts of the world. The transmission of *Besnoitia* spp. remained a mystery until Wallace and Frenkel (1975) reported that cats fed tissues of rodents infected with a rodent *Besnoitia* (*B. wallacei*) shed *Toxoplasma*-like oocysts (Frenkel, 1977). Earlier, Peteshev *et al*. (1974) from Kazakhstan had reported that cats fed tissues of cows infected with *B. besnoiti* had shed *Besnoitia* oocysts. However, their findings could not be confirmed (Rommel, 1975). Subsequently, cats were shown to be the definitive hosts for *B. darlingi* of the American opossum (Smith and Frenkel, 1977; Dubey *et al*. 2002*a*) and for a new species, *B. oryctofelisi* that we isolated from a rabbit in Argentina (Dubey *et al*. 2003). Thus, 3 species of *Besnoitia, B. wallacei, B. darlingi, and B. oryctofelisi* have *T. gondii*-like oocysts in the faeces of cats.

## CRYPTOSPORIDIAL OOCYSTS IN FAECES OF CATS AND DOGS

*Cryptosporidia* spp. are coccidian parasites. Tyzzer originally described 2 species, *C. parvum*, and *C. muris*, as parasites of rodents (Tyzzer, 1910, 1912). After the discovery of the Human Immunodeficiency Virus and the disease Acquired Immunodeficiency Syndrome (AIDS), cryptosporidia were recognized as an important opportunistic pathogen for AIDS. Currently there are numerous species and genotypes of *Cryptosporidium*, including *C. felis* (Iseki, 1979) and *C. canis* (Fayer *et al*. 2001) specifically described as feline and canine parasites. However, human cryptosporidial species can infect other animals and animal cryptosporodial species can infect humans (reviewed by Santin and Trout, 2008).

## CONCLUSION

It is clear from the above discussion that *I. bigemina* observed by Wenyon and others was a mixture of many organisms. The unsporulated 10–15 $\mu$m sized oocysts in cat faeces will be similar to *T. gondii, H. hammondi, Besnoitia* spp. (*B. wallacei, B. oryctofelisi, B. darlingi*), *H. heydorni*, and *N. caninum*. The sporulated oocysts in cat and dog faeces were probably *Sarcocystis* species (at least 31 species). This group of organisms causes serious economic losses in animals and enormous human suffering.

In the last 25 years, the medical and veterinary importance of cat and dog coccidians became recognized. Although we have learnt much regarding these parasites in the last 40 years, many challenges remain including the life cycles of *Besnoitia besnoiti, Sarcocystis canis, and Neospora hughesi*. Studies of these coccidians have been a great learning experience for me. My own journey on coccidiosis started with the description of coccidian oocysts in the Indian jungle cat (*Felis chaus*) in 1962 (Dubey and Pande, 1963), and studies on cat coccidia have no end in sight. In the *Felis chaus* paper, I described several species of *Eimeria*, *Isospora rivolta*, and

*Cryptosporodium* sp. Currently, all *Eimeria* spp. in cat and dog faeces are considered pseudoparasites (passing through the gut after eating other animals or faeces), and the *Cryptosporodium* sp. that I reported in 1963 was probably a *Sarcocystis* sp. based on its size.

I would like to dedicate this paper to the late Professor Norman D. Levine, who was a mentor and a friend. Although I never worked in his laboratory, he edited many of my papers and taught me morphological description of coccidian stages, as early as 1962.

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